2 SYNOPSIS

Name of Sponsor/Company: Ipsen Ltd	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For national authority use only)*
Name of Product: Somatuline® Autogel®		
Name of Active Ingredient(s): Lanreotide acetate		
Title of study: An observational, multicentre, open label, non-interventional programme to assess the long-term safety and efficacy of Somatuline® Autogel® in the treatment of neuroendocrine tumours when administered by patients or their partners ("Home Injection Group") or administered by Healthcare Professionals		
Investigators: 4 hospital clinicians in Australia contributed patients across 5 study centres		
Study centre(s): PPD [redacted]		
Publication (reference): None at the time of writing this report		
Studied period (years): Date of first enrolment: 05 August 2009 Date of last completed: 17 December 2013		**Phase of development**: Post marketing

Objectives:

Primary:

To assess the safety and local tolerability of the long-term use of Somatuline Autogel when administered by patients or their partners ("Home Injection Group") and the safety and local tolerability in patients receiving their injection from a Healthcare Professional (HCP) ("Reference Group").

Secondary:

To assess the efficacy of the long-term use of Somatuline Autogel in both groups.

To evaluate the training requirements for patients/partners to perform home injection of Somatuline Autogel.

To evaluate the acceptability of home injections to patients, partners and healthcare professionals.

Methodology:

This was an observational (non-interventional), multicentre post marketing surveillance programme. Patients who had been established on a stable dose of Somatuline Autogel for at least 4 months before entering the programme were asked if they wished to commence home (self or partner) injections. The decision was taken prior to, and independently of, the decision to participate in this post-marketing surveillance (PMS) programme. Patients who were enrolled in this PMS programme and chose to have their injections self or

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partner administered were included in the Home Injection Group, and patients who chose to receive their injections from a healthcare professional (HCP) were included in the Reference (HCP) Group. Patients could switch from home injection to HCP injection or from HCP injection to home injection during the observation period.

Number of patients (planned and analysed):

It was planned that approximately 30 patients would be enrolled in this PMS programme. The number of patients enrolled into each group was not mandated. At the end of the data collection period, 25 patients were enrolled and 24 patients were included in the intention-to-treat (ITT)/Safety Population. Of the 24 patients included in the analysis, 5 patients were included in the Home Injection Group and 19 patients were included in the Reference (HCP) Group).

Diagnosis and criteria for inclusion:

Eligible patients were at least 18 years of age and had a diagnosis of neuroendocrine tumour (NET) for which they had received treatment with Somatuline Autogel at a stable dose for at least 4 months. All patients gave written informed consent for their data to be included in the database for this PMS programme and any subsequent analysis. Patients who chose to be in the Home Injection Group had to be able to store Somatuline Autogel safely in a refrigerator in their own home, and either to collect it from their General Practitioner (GP) or Pharmacy on a monthly basis, or to receive the medication by a home delivery service.

Patients who were pregnant or breast-feeding were excluded from the study unless the treating clinician determined that continued treatment with Somatuline Autogel was clearly needed.

Study product dose, mode of administration and batch numbers:

Somatuline Autogel was supplied in pre-filled ready-for-use syringes containing 60, 90 or 120 mg lanreotide as acetate. Study medication was administered by deep subcutaneous injection into either the superior external quadrant of the buttock (HCP or partner injections) or the upper, outer thigh (self injections). Injections could be given by an HCP or by an appropriately trained friend or relative of the patient. Patients who were well motivated and had received appropriate training could self-administer the product.

Injections were generally administered every 28 days. The dose and frequency of administration was determined by the treating clinician in accordance with usual medical practice.

Study medication was obtained from commercial stock and batch numbers were not

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recorded.

Duration of treatment:

Somatuline Autogel is a long-term treatment and no duration of treatment was defined. Participation in the PMS programme for each patient could be up to 4 years, depending on the timing of their enrolment. Participation in the programme ended for all patients 2 years after the last patient was enrolled in the programme.

Reference therapy dose, mode of administration and batch numbers:

There was no comparator compound in this study. The Reference Group consisted of patients whose Somatuline Autogel (60, 90, or 120 mg) was administered by their usual HCP.

Criteria for evaluation:

Safety endpoints:

- Incidence of related treatment-emergent adverse events (TEAEs).
- Incidence of related serious adverse events (SAEs).
- Concomitant medications, therapies and surgical procedures.
- Other assessment results where available including; liver and gall bladder ultrasound imaging, vital signs (heart rate, blood pressure, weight, height).

Efficacy endpoints:

- Peptide markers: chromogranin A, chromogranin B, pancreatic polypeptide, somatostatin, glucagon, vasoactive intestinal peptide. These peptide markers are used in the diagnosis and monitoring of patients who have gastroenteropancreatic neuroendocrine (including carcinoid) tumours NETS.
- 24-hour 5- hydroxyindoleacetic acid (5-HIAA) urine levels.
- Tumour size.
- NET symptoms.

Additional endpoints:

- Training evaluations for patients in the Home Injection Group, including
  - Number of training sessions required.
  - Nature of training sessions required.
  - Length of training sessions.
  - Supportive material or documentation used.

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- Outcome of training session (patient/partner qualified or not qualified to perform home injections).

- Tolerability evaluations through patient reported comments.
- Acceptability evaluations, including:
  - The proportion of patients/partners who successfully qualified to perform home injections.
  - The proportion of patients who discontinued home injection after successfully qualifying to perform them.
  - Treatment compliance.
- Any other issues with administration of injections.

Statistical methods:

This was an observational programme. Therefore, no formal statistical analysis was planned or performed. All data were summarised descriptively by administration group and/or by dose and injection interval as appropriate.

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Results:

Patients:

Twenty-five patients were enrolled in the PMS programme, and 24 patients were included in the analysis: 5 patients in the Home Injection Group and 19 patients in the Reference (HCP) Group. Fourteen patients (58.3%) were male and 10 patients (41.7%) were female. Mean age was 71.5 years and ranged between 60 and 84 years. All of the patients were Caucasian/White.

Safety:

Overall exposure to treatment in this PMS programme ranged between approximately 3.7 months (14.6 weeks) and approximately 3.9 years (205.1 weeks). Median exposure was approximately 2.8 years (146.6 weeks): approximately 3 years 4 months (171.7 weeks) in the Home Injection Group and 3 years 9 months (142.1 weeks) in the Reference (HCP) Group.

A total of 17 related TEAEs were reported for 7 patients (29.2%): 2 related TEAEs were reported for 2 patients (40.0%) in the Home Injection Group, and 15 related TEAEs were reported for 5 patients (26.3%) in the Reference (HCP) Group. The most frequently reported related TEAEs were: diarrhoea, fatigue, and injection site pain (2 patients, 8.3% for each related TEAE). The other TEAEs were all single cases (4.2%) and were: abdominal pain, abdominal pain upper, pancreatitis, injection site discomfort, injection site mass, weight decreased, and flushing.

There were no related deaths, dose reductions or discontinuations related to the use of Somatuline Autogel. One patient in the Home Injection Group had a related SAE of acute, severe pancreatitis, which is a recognised adverse effect of lanreotide. Three moderate related TEAEs were reported: injection site mass, abdominal pain upper, and diarrhoea. The remaining related TEAEs were mild.

There were no indications of a relationship between dose or duration of treatment and the frequency or intensity of TEAEs.

There were 5 patients with injection tolerance data. One patient reported severe haematoma, moderate tenderness, and moderate pain at one visit during the 6-month period. All other injection tolerance data in the 4 patients with data were mild or absent.

There were no clinically significant changes in laboratory values or physical examinations, including vital signs that were reported as related TEAEs.

Other information:

Patients in the Home Injection Group were considered to have received adequate training for home injection and were qualified to perform it after up to 3 training sessions.

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Overall, mean chromogranin A levels increased between pre active study to the last visit by 776.9 pmol/L, however, the variability in the data was high (SD 13908.9 pmol/L, n=13). There were 2 patients (11.1%) with abnormal, clinically significant chromogranin A values at the last visit. One patient had abnormal, clinically significant chromogranin A values both pre-active study and at last visit, and the other patient had no data pre-active study. Mean (SD) 5-HIAA levels increased between pre-active study to the last visit by 48.6 µmol/24 hours (113.5 µmol/24 hours; n=5). There were no patients with a change from normal or abnormal not clinically significant 5-HIAA values pre-active study to abnormal clinically significant values at the last visit.

No data were recorded for chromogranin B, pancreatic polypeptide, glucagon, somatostatin, or vasoactive intestinal peptide.

There were 3/5 patients (60.0%) in the Home Injection Group and 12/19 patients (63.2%) in the Reference (HCP) Group with NET symptoms assessed at both the pre-active study visit and at last visit. Shifts in NET symptoms indicated both improvements and worsening.

None of the patients in the Home Injection Group switched to HCP injection, although 1 patient had intermittent injections administered by an HCP when he was attending the clinic.

Tumour size was not collected after the baseline visit, therefore, no analysis was performed.

Conclusion:

There were no new safety findings in this PMS Programme.

Date of report: 18 April 2015